ORIGINAL ARTICLE VIROLOGY

2009 pandemic H1N1-associated myocarditis in a previously healthy adult

S. Haessler[1], A. Paez[1], M. Rothberg[2] and T. Higgins[3]

1) *Infectious Diseases Division,* 2) *Department of Internal Medicine and* 3) *Critical Care Division, Tufts University School of Medicine, Baystate Medical Center, Springfield, MA, USA*

Abstract

Influenza infection most commonly affects the upper and lower respiratory tracts, but can involve extrapulmonary sites, including the myocardium. We report on a case of myocarditis caused by documented 2009 pandemic H1N1 influenza in a previously healthy adult, and review the literature on influenza myocarditis.

Keywords: Extrapulmonary influenza, myocarditis, pandemic influenza
Original Submission: 19 May 2010; **Accepted:** 10 June 2010
Editor: D. Raoult
Article published online: 15 July 2010
Clin Microbiol Infect 2011; **17:** 572–574
10.1111/j.1469-0691.2010.03315.x

Corresponding author: S. Haessler, Infectious Diseases Division, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199, USA
E-mail: Sarah.Haessler@bhs.org

In September 2009, a 24-year-old African American female who was healthy except for a history of benign cystic brain lesion since childhood presented to our emergency department with fatigue, light-headedness, dry cough, anorexia, vomiting, rhinorrhoea, and weakness resulting in a fall. She was afebrile, with a heart rate of 140 beats/min, a respiratory rate of 21/min and a blood pressure of 74/50 mmHg supine and 81/62 mmHg sitting. Physical examination showed normal mentation, clear lungs, and sinus tachycardia without murmur or extra heart sounds. A chest radiograph, was normal and an echocardiogram showed only sinus tachycardia. Other findings were as follows: white blood cell count, 12.7 000/mm^3 (84.4% neutrophils and 10.9% lymphocytes); serum creatinine, 0.7 mg/dL; alkaline phosphatase, 47 units; aspartate transaminase, 19 units/L; alanine transaminase, 9 units/L; and total bilirubin, 0.3 mg/dL. The initial total creatine phosphokinase (CPK) level was 204 units/L, and the troponin T level was 0.02 ng/mL. She was noted to be agitated, and had two tonic–clonic seizures. She was admitted to the intensive-care unit. A two-dimensional echocardiogram showed marked global hypokinesis with a left ventricular ejection fraction of 10–15% and a small to moderate, free-flowing pericardial effusion circumferential to the heart (Fig. 1). A repeat echocardiogram showed low-voltage QRS, diffuse ST elevation and sinus tachycardia (Fig. 2).

Past medical history was significant for a brain cyst diagnosed at age 5 years with hydrocephalus and increased intracranial pressure requiring one episode of drainage in childhood. The patient had one episode of seizure at age 12 years. She had pre-eclampsia during pregnancy, and underwent tubal ligation after delivery. She had no sick contacts, or recent travel. She did not smoke, consume alcohol, or use illicit drugs. Her 5-year-old and 1-year-old children were healthy. She took no medications.

Droplet and contact isolation precautions were implemented, according to the hospital infection control protocol. The patient was started on oseltamivir oral solution 75 mg twice daily for 5 days. A nasopharyngeal influenza A/B swab (BD Directigen EZ Flu A+B Test) was positive for influenza A virus, and this was confirmed to be the 2009 pandemic H1N1 strain by the Massachusetts State Laboratory, using RT-PCR.

A head computed tomography scan confirmed a known 2-cm cystic mass at the level of the foramen of Monro, with hydrocephalus but no midline shift. A ventricular drain was placed because of seizures and suspected intracranial hypertension, and mental status improved. A cerebral spinal fluid (CSF) sample contained 1 white blood cell per mm^3, 73 red blood cells per mm^3, 5 mg/dL of total protein and 133 mg/dL of glucose. CSF Gram stain showed no organisms and no growth on culture. CSF enterovirus PCR findings were negative.

On day 2, a two-dimensional echocardiogram showed persistent pericardial effusion with mild right atrial and

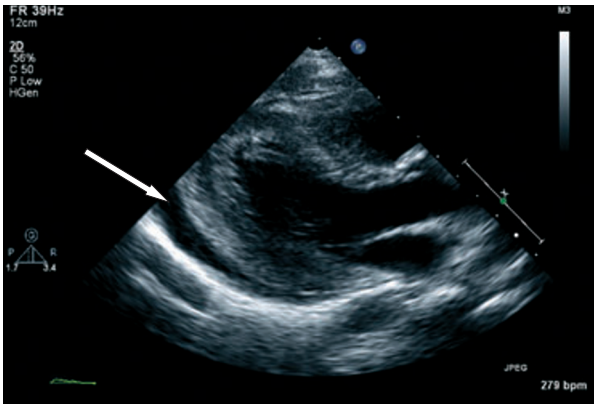

FIG. 1. Two-dimensional echocardiogram showing pericardial effusion (arrow).

ventricular collapse. An interventional radiologist was consulted, but felt that there was there was insufficient fluid to attempt drainage. A chest computed tomography scan showed bilateral upper lobe scattered small patchy opacities, and bilateral pleural effusions with adjacent atelectasis. The patient developed respiratory failure, and was intubated and mechanically ventilated in Assist-Control mode with 10-cm H_2O positive end-expiratory pressure. She required a norepinephrine drip, owing to hypotension; stroke volume (indexed) remained between 40 and 50 mL/m^2, and inotropes were not required. She developed a temperature of 38.7°C.

On days 3–6, the echocardiogram did not change. Creatinine peaked at 2.1 mg/dL. CPK peaked on day 3 at 2693 units/L, with an MB fraction of 17.7 units/L. Troponin T peaked at 0.31 ng/mL. On day 7, the ventricular drain was clamped and removed. On day 8, the patient was extubated, and a two-dimensional echocardiogram showed normalization of left ventricular systolic function, reduced pericardial effusion and pulmonary hypertension (estimated peak pressure of 45 mmHg) with moderate to severe tricuspid valve regurgitation. On day 12, she was discharged home without neurological sequelae or the need for home oxygen supplementation. Renal dysfunction, leukocytosis and the elevation in CPK resolved.

Discussion

Influenza infection is commonly associated with pulmonary complications, but may involve a number of other organ systems, including the myocardium. Our patient had clear evidence of reversible myocardial dysfunction associated with 2009 pandemic H1N1 infection. She appears to have suffered neurological consequences as well, although her history of seizure disorder in childhood makes the association with influenza less clear-cut.

Despite numerous case reports of myocarditis primarily associated with influenza A, and an early study showing that 29% of influenza A patients had symptomless myocarditis by electrocardiogram (EKG) criteria [1], the incidence of silent myocardial involvement has been shown to be low when CPK-MB fraction and troponin I and T levels are used as diagnostic criteria [2]. In a study of 152 influenza patients, none had elevated troponin levels, despite many patients having elevated levels of CPK, presumably of skeletal muscle origin [3]. Influenza RNA has been isolated from heart tissue in patients with sudden, unexpected death, but other viruses are more common [4].

The pathophysiology of influenza myocarditis, like that of other types of viral myocarditis, includes both direct viral invasion and an inflammatory reaction. In a murine model of influenza A myocarditis, inflammatory cell infiltration of the myocardium developed between days 3 and 7, and showed healing by day 9. Platelet thrombi developed in the capillaries

FIG. 2. Echocardiogram showing mild diffuse ST segment elevation in the precordial leads.

between days 3 and 5, and left ventricular dysfunction was shown between days 3 and 9, resolving by day 14. Electron microscopy showed degenerating myosites, macrophages and lymphocytes in close communication, implying that the mechanism of injury involves both direct viral invasion and cytotoxic immunological interactions [5].

Reports of myocarditis associated with 2009 pandemic H1N1 appear to be extremely rare. One case series described four children with fulminant myocarditis, with one dying and two requiring extracorporeal membrane oxygenation [6], and myocarditis was mentioned as a complication in five of 74 adult patients in one series examining cases with severe disease and acute respiratory distress syndrome in China [7]. Seizures and other neurological complications have been well documented [8]. The 2009–2010 pandemic has been remarkable for the large number of severe complications among young, previously healthy, patients. Too few cases of myocarditis resulting from seasonal influenza have been reported for risk factors to be determined. However, in at least several reported cases, the patients were young and otherwise healthy [9–12].

Treatment is largely supportive. Antiviral therapy is unproven, but might be helpful if started early. Immunosuppressive therapy is unlikely to be helpful, and many patients will make a full recovery within several weeks. For the remainder, the mortality rate appears to be high [13].

Transparency Declaration

There are no funding sources or conflicts of interest to disclose for any of the authors.

References

1. Lewes D, Rainford DJ, Lane WF. Symptomless myocarditis and myalgia in viral and Mycoplasma pneumoniae infections. *Br Heart J* 1974; 36: 924–932.
2. Ison M, Campbell V, Rembold C, Dent J, Hayden F. Cardiac findings during uncomplicated acute influenza in ambulatory adults. *Clin Infect Dis* 2005; 40: 415–422.
3. Greaves K, Oxford JS, Price CP, Clarke GH, Crake T. The prevalence of myocarditis and skeletal muscle injury during acute viral infection in adults: measurement of cardiac troponins I and T in 152 patients with acute influenza infection. *Arch Intern Med* 2003; 163: 165–168.
4. Cioc AM, Nuovo GJ. Histologic and in situ viral findings in the myocardium in cases of sudden, unexpected death. *Mod Pathol* 2002; 15: 914–922.
5. Kotaka M, Kitaura Y, Deguchi H, Kawamura K. Eperimental influenza A virus myocarditis in mice. *Am J Pathol* 1990; 136: 409–419.
6. Bratincsák A, El-Said H, Bradley J, Shayan K, Grossfeld P, Cannavino C. Fulminant myocarditis associated with pandemic H1N1 influenza A virus. *J Am Coll Cardiol* 2010; 55: 928–929, published online Feb 10.
7. To KKW, Hung IFN, Li IWS *et al.* Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis* 2010; 50: 850–859.
8. Evans AS, Agadi S, Siegel JD *et al.* Neurologic complications associated with novel influenza A (H1N1) virus infection in children—Dallas, Texas, May 2009. *MMWR* 2009; 58: 773–778.
9. Onitsuka H, Imamura T, Miyamoto N *et al.* Clinical manifestations of influenza A myocarditis during the influenza epidemic of winter 1998–1999. *J Cardiol* 2001; 37: 315–323.
10. Nolte K, Alakija P, Oty G *et al.* Influenza A virus infection complicated by fatal myocarditis. *Am J Forensic Med Pathol* 2000; 21: 375–379.
11. Engblom E, Ekfors T, Meurman O, Toivanen A, Nikoskelainen J. Fatal influenza A myocarditis with isolation of virus from the myocardium. *Acta Med Scand* 1983; 213: 75–78.
12. Mamas M, Nair S, Fraser D. Cardiac tamponade and heart failure as a presentation of influenza. *Exp Clin Cardiol* 2007; 12: 214–216.
13. Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation* 2003; 107: 857–863.